

CLAIMS:

1. A method of comparing at least one chromosome or part thereof from a cell with a first karyotype with the corresponding chromosome or part thereof
5 from a cell with a second karyotype, the method including the steps of:
 - (a) amplifying DNA from an isolated chromosome or part of an isolated chromosome;
 - (b) attaching the amplified DNA to a solid substrate;
 - (c) amplifying DNA from one or more cells with a first karyotype and
10 amplifying DNA from one or more cells with a second karyotype;
 - (d) labelling the amplified DNA from the one or more cells with a first karyotype with a first label, and labelling the amplified DNA from the one or more cells with a second karyotype with a second label, wherein the first and second labels are detectably different;
 - 15 (e) hybridizing the amplified and labelled DNA from the one or more cells with a first karyotype to the amplified DNA attached to the solid substrate, and hybridizing the amplified and labelled DNA from the one or more cells with a second karyotype to the amplified DNA attached to the solid substrate; and
 - 20 (f) comparing the relative amount of first and second labels hybridized to the amplified DNA attached to the solid substrate.
2. A method according to claim 1; wherein the amplifying DNA from an isolated chromosome or a part of an isolated chromosome is randomly primed
25 amplification.
3. A method according to claim 2; wherein the randomly primed amplification includes the use of a degenerate oligonucleotide primer.
- 30 4. A method according to claim 3, wherein the degenerate oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

5. A method according to any one of claims 1 to 4, wherein the isolated chromosome is a chromosome isolated by microdissection or flow cytometry.
6. A method according to any one of claims 1 to 4, wherein the part of an
5 isolated chromosome is a cloned fragment of a chromosome.
7. A method according to claim 6, wherein the amplified DNA from a part of an isolated chromosome is depleted of non-chromosomal sequences.
- 10 8. A method according to any one of claims 1 to 7, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is depleted of repetitive sequences and/or sequences that over represented due to the amplifying of the DNA.
- 15 9. A method according to claim 8, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is depleted of repetitive sequences.
10. A method according to claim 9, wherein the repetitive sequences are
20 Cot-1 sequences.
11. A method according to any one of claims 1 to 10, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is size selected prior to attaching the amplified DNA to the solid substrate.
- 25 12. A method according to claim 11, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is size selected for DNA of a size of less than 10 kb.
- 30 13. A method according to claim 11, wherein the amplified DNA from the isolated chromosome or part of an isolated chromosome is size selected for DNA of a size of less than 3 kb.

14. A method according to any one of claims 1 to 13, wherein the amplifying of DNA from one or more cells with a first karyotype and the amplifying of DNA from one or more cells with a second karyotype is randomly primed amplification.
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15. A method according to claim 14, wherein the randomly primed amplification includes the use of a degenerate oligonucleotide primer.
16. A method according to claim 15, wherein the degenerate
10 oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.
17. A method according to any one of claims 1 to 16, wherein the amplified DNA from one or more cells with a first karyotype and the amplified DNA from
15 one or more cells with a second karyotype are both depleted of repetitive sequences.
18. A method according to claim 17, wherein the repetitive sequences are Cot-1 sequences.
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19. A method according to any one of claims 1 to 18, wherein the amplified DNA from one or more cells with a first karyotype is DNA amplified from 1 to 20 cells.
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20. A method according to any one of claims 1 to 18, wherein the amplified DNA from one or more cell with a first karyotype is DNA amplified from a single cell.
21. A method according to any one of claims 1 to 19, wherein the one or
30 more cells with a first karyotype is an embryonic cell, a foetal cell, a germ cell, a cancerous cell, or a polar body.

22. A method according to claim 20, wherein the single cell is an embryonic cell, an oocyte, or a polar body.
23. A method according to any one of claims 1 to 22, wherein the one or
5 more cells with a second karyotype is a cell of the same type as the one or more cells with a first karyotype.
24. A method according to any one of claims 1 to 23, wherein the amplified
DNA from one or more cells with a second karyotype is DNA amplified from the
10 same number of cells as the one or more cells with a first karyotype.
25. A method according to any one of claims 1 to 24, wherein the
amplification of DNA from the isolated chromosome or part of the isolated
chromosome further includes amplification of a specific chromosomal region.
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26. A method according to any one of claims 1 to 25, wherein the
amplification of DNA from one or more cells with a first karyotype and the
amplification of DNA from one or more cells with a second karyotype further
includes amplification of the same specific chromosomal region.
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27. A method according to any one of claims 1 to 26, wherein the first label is
Cy3-dUTP and the second label is Cy5-dUTP.
28. A method according to any one of claims 1 to 27, wherein the method is
25 used for pre-implantation diagnosis of an embryo or an oocyte.
29. A method according to any one of claims 1 to 27, wherein the method is
used for the prenatal diagnosis of a foetus for a chromosomal abnormality.
30. A method of detecting a chromosomal abnormality in a cell with an
unknown karyotype, the method including the steps of:
(a) amplifying DNA from an isolated chromosome or part of an isolated
chromosome;

- (b) attaching the amplified DNA to a solid substrate;
(c) amplifying DNA from one or more cells with an unknown karyotype and amplifying DNA from one or more cells with a reference karyotype;
(d) labelling the amplified DNA from one or more cells with the unknown karyotype with a first label, and labelling the amplified DNA from one or more cells with the reference karyotype with a second label, wherein the first and second labels are detectably different;
(e) hybridising the amplified and labelled DNA from the one or more cells with an unknown karyotype to the amplified DNA attached to the solid substrate, and hybridising the amplified and labelled DNA from the one or more cells with a reference karyotype to the amplified DNA attached to the solid substrate; and
(f) detecting the presence of a chromosome abnormality in the cell with the unknown karyotype by comparing the relative amount of the first label hybridised to the amplified DNA attached to the solid substrate to the amount of a second label hybridised to the amplified DNA attached to the solid substrate.

31. A method according to claim 30, wherein the amplifying DNA from an isolated chromosome or a part of an isolated chromosome is randomly primed amplification.

32. A method according to claim 31, wherein the randomly primed amplification includes the use of a degenerate oligonucleotide primer.

33. A method according to claim 32, wherein the degenerate oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

34. A method according to any one of claims 30 to 33, wherein the isolated chromosome is a chromosome isolated by microdissection or flow cytometry.

35. A method according to any one of claims 30 to 33, wherein the part of an isolated chromosome is a cloned fragment of a chromosome.
36. A method according to claim 35, wherein the amplified DNA from a part
5 of an isolated chromosome is depleted of non-chromosomal sequences.
37. A method according to any one of claims 30 to 36, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is depleted of repetitive sequences and/or sequences that over represented due
10 to the amplifying of the DNA.
38. A method according to claim 37, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is depleted of repetitive sequences.
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39. A method according to claim 38, wherein the repetitive sequences are Cot-1 sequences.
40. A method according to any one of claims 30 to 39, wherein the
20 amplified DNA from an isolated chromosome or part of an isolated chromosome is size selected prior to attaching the amplified DNA to the solid substrate.
41. A method according to claim 40, wherein the amplified DNA from an isolated chromosome or part of an isolated chromosome is size selected for
25 DNA of a size of less than 10 kb.
42. A method according to claim 40, wherein the amplified DNA from the isolated chromosome or part of an isolated chromosome is size selected for DNA of a size of less than 3 kb.
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43. A method according to any one of claims 30 to 42, wherein the amplifying of DNA from one or more cells with an unknown karyotype and the

amplifying of DNA from one or more cells with a reference karyotype is randomly primed DNA amplification.

44. A method according to claim 43, wherein the amplifying includes the use of a degenerate oligonucleotide primer.

45. A method according to claim 44, wherein the degenerate oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

46. A method according to any one of claims 30 to 45, wherein the amplified DNA from one or more cells with an unknown karyotype and the amplified DNA from one or more cells with a reference karyotype are both depleted of repetitive sequences.

47. A method according to claim 46, wherein the repetitive sequences are Cot-1 sequences.

48. A method according to any one of claims 30 to 47, wherein the amplified DNA from one or more cells with an unknown karyotype is DNA amplified from 1 to 20 cells.

49. A method according to any one of claims 30 to 47, wherein the amplified DNA from one or more cells with an unknown karyotype is DNA amplified from a single cell.

50. A method according to any one of claims 30 to 48, wherein the one or more cells with an unknown karyotype is an embryonic cell, a foetal cell, a germ cell, a cancerous cell, or a polar body.

51. A method according to claim 50, wherein the single cell is an embryonic cell, an oocyte, or a polar body.

52. A method according to any one of claims 30 to 51, wherein the one or more cells with a reference karyotype is a cell of the same type as the one or more cells with an unknown karyotype.
- 5 53. A method according to any one of claims 30 to 52, wherein the amplified DNA from the one or more cells with a reference karyotype is DNA amplified from the same number of cells as the one or more cells with an unknown karyotype.
- 10 54. A method according to any one of claims 30 to 53, wherein the amplification of DNA from an isolated chromosome or a part of an isolated chromosome further includes amplification of a specific chromosomal region.
- 15 55. A method according to any one of claims 30 to 54, wherein the amplification of DNA from one or more cells with an unknown karyotype and the amplification of DNA from one or more cells with a reference karyotype further includes amplification of the same specific chromosomal region.
- 20 56. A method according to any one of claims 30 to 55, wherein the first label is Cy3-dUTP and the second label is Cy5-dUTP.
57. A method according to any one of claims 30 to 56, wherein the method is used for pre-implantation diagnosis of an embryo or an oocyte.
- 25 58. A method according to any one of claims 30 to 56, wherein the method is used for the prenatal diagnosis of a foetus for a chromosomal abnormality.
- 30 59. A nucleic acid attached to a solid substrate, wherein the nucleic acid is derived from an isolated chromosome or part of an isolated chromosome and the nucleic acid is depleted of repetitive sequences.

60. A nucleic acid according to claim 59, wherein the nucleic acid is derived from amplification of an isolated chromosome or part of an isolated chromosome.

5 61. A nucleic acid according to claim 60, wherein the amplification from an isolated chromosome or a part of an isolated chromosome is randomly primed amplification.

62. A nucleic acid according to claim 61, wherein the amplification from an
10 isolated chromosome or a part of an isolated chromosome includes the use of a degenerate oligonucleotide primer.

63. A nucleic acid according to claim 62, wherein the degenerate
oligonucleotide primer consists of the sequence 5'-
15 CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

64. A nucleic acid according to any one of claims 59 to 63, wherein the
isolated chromosome is a chromosome isolated by microdissection or flow
cytometry.

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65. A nucleic acid according to any one of claims 59 to 63, wherein the part
of an isolated chromosome is part of a chromosome isolated by microdissection
or flow cytometry.

25 66. A nucleic acid according to any one of claims 59 to 63, wherein the part
of an isolated chromosome is a cloned fragment of a chromosome.

67. A nucleic acid according to claim 66, wherein the nucleic acid is also
depleted of non-chromosomal sequences.

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68. A nucleic acid according to any one of claims 60 to 67, wherein the
amplified DNA from an isolated chromosome or part of an isolated chromosome
is also depleted of sequences that are over represented due to amplification.

69. A nucleic acid according to any one of claims 59 to 68, wherein the repetitive sequences are Cot-1 sequences.

5 70. A nucleic acid according to any one of claims 59 to 69, wherein the amplified nucleic acid from an isolated chromosome or part of an isolated chromosome is size selected.

71. A nucleic acid according to claim 70, wherein the amplified nucleic acid
10 from an isolated chromosome or part of an isolated chromosome is size selected for a size of less than 10 kb.

72. A nucleic acid according to claim 70, wherein the amplified nucleic acid
15 from the isolated chromosome or part of an isolated chromosome is size selected for a size of less than 3 kb.

73. A nucleic acid according to any one of claims 59 to 72, wherein the nucleic acid attached to the substrate is a target for hybridization.

20 74. A nucleic acid according to claim 73, wherein the nucleic acid attached to the substrate is a target for comparative genomic hybridisation.

75. An array of nucleic acids, the array including one or more nucleic acids attached to a solid substrate according to any one of claims 59 to 74.

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76. A nucleic acid attached to a solid substrate, wherein the nucleic acid is derived from randomly primed amplification of an isolated chromosome or part of an isolated chromosome, and the nucleic acid is depleted of one or more of repetitive sequences, non-chromosomal sequence or sequences that are over-
30 represented due to the amplification.

77. A nucleic acid according to claim 76, wherein the randomly primed amplification includes the use of a degenerate oligonucleotide primer.

78. A nucleic acid according to claim 77, wherein the degenerate oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

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79. A nucleic acid according to any one of claims 76 to 78, wherein the isolated chromosome is an chromosome isolated by microdissection or flow cytometry.

10 80. A nucleic acid according to any one of claims 76 to 78, wherein the part of an isolated chromosome is a part of a chromosome isolated by microdissection or flow cytometry.

15 81. A nucleic acid according to any one of claims 76 to 78, wherein the part of an isolated chromosome is a cloned fragment of a chromosome.

82. A nucleic acid according to any one of claims 76 to 81, wherein the repetitive sequences are Cot-1 sequences.

20 83. A nucleic acid according to any one of claims 76 to 82, wherein the non-chromosomal sequences are bacterial sequences.

25 84. A nucleic acid according to any one of claims 76 to 83, wherein the amplified nucleic acid from the isolated chromosome or part of an isolated chromosome is size selected.

85. A nucleic acid according to claim 84, wherein the amplified nucleic acid from an isolated chromosome or part of an isolated chromosome is size selected for a size of less than 10 kb.

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86. A nucleic acid according to claim 84, wherein the amplified nucleic acid from the isolated chromosome or part of an isolated chromosome is size selected for a size of less than 3 kb.

87. A nucleic acid according to any one of claims 76 to 86, wherein the nucleic acid attached to the solid substrate is a target for hybridisation.

5 88. A nucleic acid according to claim 87, wherein the nucleic acid attached to the solid substrate is a target for comparative genomic hybridisation.

89. An array of nucleic acids attached to a solid substrate, the array including one or more nucleic acids attached to a solid substrate according to
10 any one of claims 76 to 88.

90. A nucleic acid derived from randomly primed amplification of an isolated chromosome or part of an isolated chromosome, wherein the nucleic acid is depleted of repetitive sequences.

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91. A nucleic acid according to claim 90, wherein the randomly primed amplification includes the use of a degenerate oligonucleotide primer.

92. A nucleic acid according to claim 91, wherein the degenerate
20 oligonucleotide primer consists of the nucleotide sequence 5'-CCGACTCGAGNNNNNNATGTGG-3', N being any nucleotide.

93. A nucleic acid according to any one of claims 90 to 92, wherein the isolated chromosome is isolated by microdissection or flow cytometry.

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94. A nucleic acid according to any one of claims 90 to 92, wherein the part of an isolated chromosome is part of a chromosome isolated by microdissection or flow cytometry.

30 95. A nucleic acid according to any one of claims 90 to 92, wherein the part of an isolated chromosome is a cloned fragment of a chromosome.

96. A nucleic acid according to claim 95, wherein the nucleic acid is also depleted of non-chromosomal sequences.

97. A nucleic acid according to any one of claims 91 to 96, wherein the
5 nucleic acid is further depleted of sequences that are over represented due to amplification.

98. A nucleic acid according to any one of claims 90 to 97, wherein the
10 repetitive sequences are Cot-1 sequences.

99. A nucleic acid according to any one of claims 90 to 98, wherein the nucleic acid is size selected.

100. A nucleic acid according to claim 99, wherein the nucleic acid is size
15 selected for a size of less than 10 kb.

101. A nucleic acid according to claim 88, wherein the nucleic acid is size selected for a size of less than 3 kb.

20 102. A nucleic acid according to any one of claims 90 to 101, wherein the nucleic acid is a target nucleic acid for hybridisation.

103. A nucleic acid according to claim 102, where the nucleic acid is a target
25 nucleic acid for comparative genomic hybridisation.

104. A method of comparing at least one chromosome or part thereof from a single cell with a first karyotype with the corresponding chromosome or part thereof from a cell with a second karyotype, the method including the steps of:

- 30 (a) randomly amplifying DNA from an isolated chromosome or part of an isolated chromosome;
(b) attaching the amplified DNA to a solid substrate;

- (c) randomly amplifying DNA from a single cell with a first karyotype and randomly amplifying DNA from one or more cells with a second karyotype;
- 5 (d) labelling the amplified DNA from the single cell with a first karyotype with a first label, and labelling the amplified DNA from the one or more cells with a second karyotype with a second label, wherein the first and second labels are detectably different;
- 10 (e) hybridizing the amplified and labelled DNA from the single cell with a first karyotype to the amplified DNA attached to the solid substrate, and hybridizing the amplified and labelled DNA from the one or more cells with a second karyotype to the amplified DNA attached to the solid substrate; and
- (f) comparing the relative amount of first and second labels hybridized to the amplified DNA attached to the solid substrate.
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105. A method of detecting a chromosomal abnormality in a single cell with an unknown karyotype, the method including the steps of:
- (a) randomly amplifying DNA from an isolated chromosome or part of an isolated chromosome;
- 20 (b) attaching the amplified DNA to a solid substrate;
- (c) randomly amplifying DNA from a single cell with an unknown karyotype and amplifying DNA from one or more cells with a reference karyotype;
- 25 (d) labelling the amplified DNA from the single cell with an unknown karyotype with a first label, and labelling the amplified DNA from one or more cells with a reference karyotype with a second label, wherein the first and second labels are detectably different;
- 30 (e) hybridising the amplified and labelled DNA from the single cell with an unknown karyotype to the amplified DNA attached to the solid substrate, and hybridising the amplified and labelled DNA from the one or more cells with a reference karyotype to the amplified DNA attached to the solid substrate; and

(g) detecting the presence of a chromosome abnormality in the single cell with the unknown karyotype by comparing the relative amount of the first label hybridised to the amplified DNA attached to the solid substrate to the amount of a second label hybridised to the amplified DNA attached to the solid substrate.

106. A method of pre-implantation genetic diagnosis of an embryo, the method including the steps of:

- 10 (a) randomly amplifying DNA from an isolated chromosome or part of an isolated chromosome;
- (b) attaching the amplified DNA to a solid substrate;
- (c) randomly amplifying DNA from a cell from one or more embryonic cells with an unknown karyotype and amplifying DNA from one or more cells with a reference karyotype;
- 15 (d) labelling the amplified DNA from the one or more embryonic cells with an unknown karyotype with a first label, and labelling the amplified DNA from one or more cells with a reference karyotype with a second label, wherein the first and second labels are detectably different;
- 20 (e) hybridising the amplified and labelled DNA from the one or more cells with an unknown karyotype to the amplified DNA attached to the solid substrate, and hybridising the amplified and labelled DNA from the one or more cells with a reference karyotype to the amplified DNA attached to the solid substrate;
- 25 (f) detecting the presence of a chromosome abnormality in the embryo with the unknown karyotype by comparing the relative amount of the first label hybridised to the amplified DNA attached to the solid substrate to the amount of a second label hybridised to the amplified DNA attached to the solid substrate; and
- 30 (g) determining the suitability of the embryo or the oocyte for implantation by the absence of a chromosomal abnormality in the one or more embryonic cells.

107. A method of pre-implantation genetic diagnosis of an oocyte, the method including the steps of:

- 5 (a) randomly amplifying DNA from an isolated chromosome or part of an isolated chromosome;
- (b) attaching the amplified DNA to a solid substrate;
- (c) randomly amplifying DNA from a polar body of an oocyte with an unknown karyotype and amplifying DNA from one or more cells with a reference karyotype;
- 10 (d) labelling the amplified DNA from the polar body of an oocyte with an unknown karyotype with a first label, and labelling the amplified DNA from one or more cells with a reference karyotype with a second label, wherein the first and second labels are detectably different;
- 15 (e) hybridising the amplified and labelled DNA from the polar body of an oocyte with an unknown karyotype to the amplified DNA attached to the solid substrate, and hybridising the amplified and labelled DNA from the one or more cells with a reference karyotype to the amplified DNA attached to the solid substrate;
- 20 (f) detecting the presence of a chromosome abnormality in the polar body of an oocyte with the unknown karyotype by comparing the relative amount of the first label hybridised to the amplified DNA attached to the solid substrate to the amount of a second label hybridised to the amplified DNA attached to the solid substrate; and
- 25 (g) determining the suitability of the oocyte for implantation by the absence of a chromosomal abnormality in the polar body of the oocyte.

108. A method of prenatal diagnosis of a foetus for a chromosomal abnormality, the method including the steps of:

- 30 (a) randomly amplifying DNA from an isolated chromosome or part of an isolated chromosome;
- (b) attaching the amplified DNA to a solid substrate;

(c) randomly amplifying DNA from one or more foetal cells with an unknown karyotype and amplifying DNA from one or more cells with a reference karyotype;

5 (d) labelling the amplified DNA from the one or more foetal cells with an unknown karyotype with a first label, and labelling the amplified DNA from one or more cells with the reference karyotype with a second label, wherein the first and second labels are detectably different;

10 (e) hybridising the amplified and labelled DNA from the one or more foetal cells with an unknown karyotype to the amplified DNA attached to the solid substrate, and hybridising the amplified and labelled DNA from the one or more cells with a reference karyotype to the amplified DNA attached to the solid substrate; and

15 (f) determining the presence of a chromosome abnormality in the foetus by comparing the relative amount of the first label hybridised to the amplified DNA attached to the solid substrate to the amount of a second label hybridised to the amplified DNA attached to the solid substrate.

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